National Institute of Allergy and Infectious Diseases

BIODEFENSE WORKSHOP SUMMARY
IMMUNOSUPPRESSION AND VACCINATION IN SPECIAL POPULATIONS

May 12-13, 2004

Residence Inn Bethesda Downtown
Bethesda, Maryland

Workshop Goal

On May 12 and 13, 2004 the National Institute of Allergy and Infectious Disease (NIAID) sponsored a group[1] of physician researchers and immunologists to discuss challenges and approaches in the protection of immunocompromised individuals against infections, toxins, and potentially harmful effects of vaccines, as they relate to biodefense. Discussion from this meeting will contribute to NIAID's assessment of the state of the science regarding enhancement of innate and adaptive immune responses in immunosuppressed individuals, as this relates to improved vaccines and immunotherapies for the people in these groups. The target populations include neonates, infants, the elderly, pregnant women, and individuals with primary immunodeficiency diseases or drug-induced suppression resulting from therapy for cancer, transplantation or autoimmune diseases.

Background

The increased threat of bioterrorism and the emergence of potentially fatal diseases such as SARS and West Nile virus underscore the compelling need to develop improved treatments for protecting all segments of the human population, including immunocompromised individuals at high risk of acquiring infectious diseases. In addition to the very young and the elderly who have a natural sub-optimal immune capacity, there are a growing number of people receiving chemotherapy for cancer, or immunosuppressive drugs for transplant or autoimmune diseases. New methods must be developed that focus on both innate and acquired immunity to provide better vaccines and immune-based therapeutic agents such as adjuvants and intravenous

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immunoglobulins to protect against infection and minimize harmful side effects for these populations.

Meeting Description

In order to help identify some of the challenges that exist for vaccination of immunosuppressed groups, the workshop brought medical scientists together to discuss the research needs in the following five areas: 1) Immunosuppression and Transplantation, 2) Immunosuppression and Cancer Therapy/Bone Marrow Transplantation, 3) Aging and Immunosuppression, 4) Immunosuppression in Children and Neonates, and 5) Primary Immune Deficiency and Vaccination.

Discussion focused on the different issues each population faces, with respect both to identifying immunological deficiencies, and to possible treatments and enhancements of the immune response to vaccination.

1. Immunosuppression and Transplantation

New immunosuppressive drugs have decreased the rate of transplants. This success, however, has lead to a growing number of immunocompromised patients that are more vulnerable to infectious disease, and that are unable to be safely treated with live virus vaccines. During this session, the current parameters and future challenges for vaccination and immunotherapy of transplant patients were discussed, and the following key issues were described:

Characteristics of Immunosuppression

- Wide variations in the biological parameters of immunosuppression are observed, depending on the type of immunosuppressive drug being used. These effects include decreased T cell and B cell proliferation, inhibition of cytokine activity, and innate immune system suppression.
- The immunosuppression induced by these drugs results in less effective vaccinations, which has been shown in the cases of S. pneumoniae, Hepatitis A, Hepatitis B, and influenza vaccines.
- Variability also is seen among different age groups of transplant patients.

Current Treatment Options

- Isolation of patients from potential infectious agents, when possible.
- Use of safer or inactivated forms of the vaccinating agent (e.g., inactivated polio vaccine).
- Passive immunization (e.g., immunoglobulin treatment for measles)
- Booster immunizations in some cases to induce protective immunity closer to normal levels (e.g., Hepatitis A vaccine).

Knowledge Gaps and Future Needs

- More details about the specific cellular mechanisms targeted by immunosuppressive drug treatment regiments.

- Multiple assays to assess multiple parts of the immune system (for example, using a microchip assay to look simultaneously at the expression of genes in T cells, B cells, and antigen presenting cells in immunosuppressed vs. non-immunosuppressed patients).
- Data on safety, efficacy, immunogenicity, and optimal timing of vaccinations. Such studies might include measures of immune protection in various hosts after infection or immunization for common and bioterrorism-related infectious diseases.
- Data regarding immune status of transplant patients that would indicate the minimum amount of immunosuppression to minimize the risk for infection without provoking graft rejection. These include longitudinal studies on the effects of immunosuppression in transplant patients over time.
- Inter-institutional studies to increase patient numbers per study since the population base of transplant patients is relatively small, and the immune effects will vary by the immunosuppressive regiment, underlying metabolic dysfunctions, organs transplanted, and population age groups.
- Longitudinal studies on the effects of immunosuppression in transplant patients over time.
- Tests to identify and diagnose infections as they occur, e.g. gene arrays that can detect relevant microorganisms and enhance the rapidity of diagnosis of new or known pathogens for early therapy.
- A consistent set of vaccination guidelines that consider the different drug treatments and age groups of transplant patients. These guidelines will help to reduce risk and increase the effectiveness of vaccinations that are currently available.
- Consider the immunocompromised hosts as unique study populations given their susceptibility to a broad range of organisms. These "sentinel" populations may provide "early warning" for novel pathogens as they have for influenza, West Nile virus, and SARS.

2. Immunosuppression and Cancer Therapy/Bone Marrow Transplantation

Another immunosuppressed population is the growing number of patients receiving chemotherapy and bone marrow transplantation as a treatment for cancer. Bone marrow transplantation patients can be immunosuppressed due to the chemotherapy, pre-transplant T cell depletion, or immunosuppressive drug therapy after the transplant. The immunological consequences of these treatments are only beginning to be characterized. Also, very little is known about how to target cellular and molecular elements of the immune system in order to improve the host response to vaccination.

Characteristics of Immunosuppression

- All patients that receive bone marrow transplants become immunosuppressed for prolonged periods. For example, their T cell responses are below normal for at least 18 months.

- Recovery of normal numbers of phenotypically mature T cells is relatively rapid, however reconstitution of T cell *function* is delayed.
- Regeneration of a diverse T cell receptor repertoire is also delayed, and in the case of allogeneic bone marrow transplants, may be caused by mixed hematopoietic chimerism.
- Since the adaptive immune system is compromised in these transplants, patients are more dependent on their innate immune system as a defense against infection. As a result of this dependence, genetic differences between individuals, such as Toll-like receptor polymorphisms, can have a much more significant effect on the response to infections or vaccinations.

Current Treatment Options

- Additional vaccinations (or boosters) can produce antibody titers in bone marrow transplant patients that are the same as those in individuals that are not immunosuppressed.

Knowledge Gaps and Future Needs

- More precise correlations between the changes in immune function and specific aspects of the treatment of bone marrow transplant patients. For example, is the slowed development of a diverse T cell receptor repertoire due to cancer chemotherapy before bone marrow transplant, immunosuppressive drug therapy after transplant, or both?
- An understanding of the role of T cell neogenesis in the restoration of T cell immunity after bone marrow transplantation.
- An understanding of the impact of allogeneic stem cell transplantation on thymic function.
- Multi-institutional projects to get the larger number of patients needed to study polymorphisms in immune system molecules (e.g., Toll-like receptors), and correlate these differences with infectious disease susceptibility and vaccine effectiveness. This information can be used to guide treatment decisions, such as which patients are the best candidates for preventative therapies (e.g., passive immunoglobulins or vaccination).
- An understanding of the types of immune system deficiencies that exist for a variety of cancer patients, and not only those receiving bone marrow transplantation.

3. Aging and Immunosuppression

Experimental results from animal models and clinical studies have described some types of immune deficiencies that occur during aging. For example, there is evidence that T cell immunity and innate immune system function decrease with age. It is also known that elderly populations do not respond as well to new antigens as younger populations. However, characterization of the aging immune

system is not complete, and very little is known about how to increase immune responsiveness in this population.

Characteristics of Immunosuppression

- Fewer new (naïve) T cells and more memory T cells (due to life-long encounters with various pathogens).
- Decreased T cell responsiveness to stimulation through the T cell receptor (TCR) and costimulatory pathway signaling molecules.
- Decreased natural killer cell numbers and activity.
- Changing levels of cytokine production and activity, for example: decreased levels of IL-2 production (an activator of T cells) and increased levels of IL-10 (an immunosuppressive cytokine).
- Diminished macrophage and granulocyte functions.
- Diminished cellular trafficking.
- Diminished cell growth and differentiation.
- Diminished signaling in response to endogenous and exogenous stimuli.

Current Treatment Options

- More effective adjuvants may be a key factor in improving immune responses of the elderly to vaccinations. For example, several types of adjuvants are currently being tested for influenza vaccine.

Knowledge Gaps and Future Needs

- A complete understanding of the changes in expression and function of innate immune molecules that occur during aging (e.g., Toll-like receptors).
- Knowledge of how aging changes the transcription of specific molecules that affect immune function (e.g., cytokines, cytokine receptors, receptors on T cells B cells and natural killer cells, transcriptional factors that effect cell growth or apoptosis).
- Expression and functional studies of age related changes in the components of signal transduction pathways (e.g. kinases, second messengers, adaptor proteins).
- Definition of the impact of aging on the phenotype, migration, and function of dendritic cells and T cells and effects on *in vivo* dynamics of T cell activation.
- A better understanding of the linkage between innate and adaptive immunity in general, since this relationship is an important aspect in the development of better vaccines.
- Delineation of the optimum priming environment to generate effective T and B cell immune responses.
- Identification of the optimal means of formulating and delivering antigens for improved adjuvant and vaccine design.

- Determination of methods to induce and modulate the appropriate regulatory, effector, and memory T cell and B cell responses for the desired preventative or therapeutic response.
- Investigation of potential approaches for improving vaccination, such as: utilizing the products of Toll-like receptor activation to enhance local defenses; restoring expression of pathogen receptors on antigen presenting cells; or correcting altered pathways of signal transduction.

4. Immunosuppression in Children and Neonates

It is known that neonatal immune function is deficient in all immune compartments, and live virus vaccines cannot be safely administered to this population. Much more research is needed to understand what specific immunodeficiencies exist as the neonate matures, and when each of these components becomes fully functional. Treatments that are designed to boost immunity of neonates must be designed and applied with the consideration that this immune system is continuously changing and maturing. Therapies that enhance the immune response to vaccination must be properly targeted, and must also be appropriate for the stage of immune development in order to avoid unwanted effects, such as an ineffective response, development of tolerance to introduced antigens, or induction of autoimmunity.

Characteristics of Immunosuppression

- An inexperienced immune system – memory T and B cell populations are not yet established, and there are deficiencies in the innate and adaptive immune compartments.
- Lower numbers of T and B lymphocytes, compared with adults.
- Lower quantity and avidity of antibodies produced.
- Limited cytokine production: e.g., IL-2 and IFNγ from T cells.
- Absent or defective neonatal CD8 T cell responses.
- Easier tolerization to alloantigens and some pathogens**.** This is an important factor that must be considered when developing a method to manipulate the host response to vaccination in the developing immune system.

Current Treatment Options

- Treatment with cytokines to temporarily boost the immune response after vaccination. An example is the injection of recombinant IL-12 and IL-15 after measles immunization to boost the cellular immune response in infants.

Knowledge Gaps and Future Needs

- An understanding of the temporal changes that occur in this rapidly developing immune system, and of the intracellular molecular events that cause these changes.

- Methods that safely enhance the host response without increasing the chances of developing autoimmunity or inappropriate tolerance to antigens.

5. Primary Immune Deficiency and Vaccination

Characteristics of Immunosuppression

- The most well studied form is Severe Combined Immunodeficiency (SCID). There are 174 known genetic mutations that cause SCID. Most of these mutations occur in nine different genes that code for cytokine receptors, signal transduction proteins, antigen receptors, recombinase activation genes, and adenosine deaminase.
- The spectrum of T cell defects ranges from the syndrome of SCID, in which T cell function is absent, to those with combined immunodeficiency disorders (CID) in which there is some but not adequate T cell function for a normal lifespan. As a result of the lack of T cell function, B cell function is also diminished, and the response to vaccines with cellular or humoral immune defenses is compromised. These patients also have serious adverse events from the administration of live vaccines.
- In addition to the T cell and B cell immunodeficiencies that occur in SCID, natural killer cell function can also be diminished.
- In B cell immunodeficiencies such as X-linked agammaglobulinemia, T cell numbers and function are normal but there are no circulating B cells due to a mutation in the gene for a tyrosine kinase that is critical for the growth and development of B cells.
- The incidence and prevalence of primary immunodeficiency diseases is unknown. The estimates that are currently used are not reliable, because there is no standard screening process for primary immunodeficiency disease. Under-diagnosis occurs because autopsies are rarely performed on infants that may die from infections. Since some individuals may have less severe forms of primary immune deficiency that allow them to survive, they are often not diagnosed early.

Current Treatment Options

- For patients with severe combined immunodeficiency, the typical treatment is bone marrow transplant.
- Intravenous immunoglobulin replacement is used to treat patients with X-linked agammaglobulinemia, common variable immunodeficiency, and other primary immune disorders that result in immunoglobulin deficiency.

Knowledge Gaps and Future Needs

- Progress towards reducing under-diagnosis in primary immunodeficiency:

- Most of the severe primary immunodeficiency patients could be diagnosed by screening for lymphopenia or for T cell deficiency in cord blood at birth. Early diagnosis is essential for application of the most appropriate treatments at a very early age, for the avoidance of live vaccines and non-irradiated blood products, and for special protection in the event of bioterrorism. For example, when smallpox vaccine was administered to infants with SCID, they died of vaccinia gangrenosum.
- A detection method that could be used in the months after birth would be to score the patient on each hospital visit for diseases or symptoms indicative of primary immune deficiency. In this disease-code scoring system for immune deficiency, a patient that accumulates a certain score would be a candidate for extensive testing for immunodeficiency.

Conclusions

The "Immunosuppression and Vaccination in Special Populations" workshop revealed the need for 1) a better understanding of the biological mechanisms that cause immunosuppression in all immunodeficient groups, and 2) new methods and treatments to enhance the immune response of these populations to vaccinations and immune-based therapeutic strategies. In addition, this workshop identified other issues that were shared among different populations:

- There is a need for interdisciplinary research teams with diverse but complementary expertise. This integrated approach would allow investigators to maximize analysis of limited samples.
- The widely varying ages of patients receiving immunosuppressive therapy and the use of different immunosuppressive drug combinations can result in small patient study groups. In these situations, a collaborative approach may be needed to combine patients and achieve statistically significant numbers.
- Although there are differences in the types of immunosuppression that exists *among* immunosuppressed groups, there are also differences *within* immunosuppressed populations:
  - Transplant patient immunosuppression: these patients are treated with a variety of immunosuppressive drugs that, when used alone or in combination, have widely varying effects on the immune system. The age of the transplant patient also affects the immune response to vaccination.
  - Age related differences: Within developing or aging immune systems there are differences in the immune state that occur either over a period of months, in the case of developing immune systems, or years, in the case of aging immune systems. These temporal differences within each group could greatly affect the type of immune enhancing treatment to be used.

    - Primary immune deficiency: Different genetic mutations affect different components of the immune system, and treatments may need to be tailored accordingly.
- The specific nature of the bioterror agent must be considered. Different infectious agents initiate varying responses of the immune system, and this may affect how vaccines and other immunotherapies are used in these immunocompromised groups.

The discussion from this workshop revealed that there are common needs for additional research. With the knowledge gained, methods can be developed to target specific biological mechanisms that enhance the host response to vaccinations and immune-based therapies.